



TECHNICAL SERVICES MONTHLY REPORT

Nov 2022 to July 2023

TSD Approach



Service
Capabilities

On time
deliverables
Quality Work

Trouble
Shooting

Unit Process
Unit
Operations

Continuous
Improvement
s

Solvent
Yield
Capacity

New Products

Eqp. Mapping
Trail & Validation
Execution

Ongoing Projects



- Capacity Enhancement

- New Products

- Technical Support
- Troubleshooting

- New Proposals



Troubleshooting

PSD Concern in Flecainide Acetate

Product & Stage:

Flecainide Acetate Pharma (FNDA2)

Existing Situation

Requirement

Material is fine and PSD is not meeting the specification with existing process.

PSD Required D50- NLT 5 microns

Proposal:

- 1) As the requirement is higher PSD, Agitator RPM reduced from 96 to 60 RPM.
- 2) Material formation observed during the initial 15-20 min of Acetic Acid + Toluene (1 Vol) solution addition, hence Acetic Acid dilution increased by dissolving in 2 Volumes of Toluene and addition duration increased from 45-60 min. to 60-90 min.
- 3) As per existing process 5 volumes of toluene slurry is performed in GL reactor by unloading the material from ANFD- Proposed for direct slurry in ANFD without unloading the material.

Result:

PSD is meeting the requirement (D50- NLT 5 microns) after above proposed modifications.

Troubleshooting

Reaction conversion issue during Trial batch in VOR2 stage of Voxelotor

Product & Stage:	Voxelotor- VOTR2
Existing Situation	Requirement
During Suzuki Coupling Reaction, VOTR1 content by TLC sample result was more than desired specification and resulted in higher Chloromom benzaldehyde impurity in Related Substances by HPLC before drying.	Obtained VOTR1 Content by TLC result is "In-between 5 %w/w and 7.5 %w/w" as against the specification limit of NMT than 5%w/w & Chloromom benzaldehyde impurity result is 2.5% against the specification limit Not more than 1.0% in Related Substances by HPLC before drying.

Proposal:

- 1) As per Trial batch observations, Tetrakis Palladium activity was reduced due to insufficient nitrogen purging, hence proposed for installation of Two Nitrogen spargers with PTFE MOC and holes at bottom for effective Nitrogen Purging.
- 2) As per R&D suggestion Tetrakis palladium was charged at higher temperature ($55\pm 5^{\circ}\text{C}$) instead of Room Temperature. To charge palladium at 55°C , Solid Charging Hopper with Double Butterfly valve set-up was arranged.
- 3) Proposed to increase the temperature from $55\pm 5^{\circ}\text{C}$ to $90\pm 10^{\circ}\text{C}$ in 20 min as per Kilo Lab Trend by applying steam at 2.5 Kg/cm² in jacket.
- 4) Additional Purification was performed in THF+MTBE media in Trial Batch to Address Quality failure & Same was incorporated in Further batches

Result:

In-process sample VOTR1 Content by TLC result is with in the specification in 2 hrs. 45 min. ± 15 min. maintenance time and Chloromom benzaldehyde impurity is at Not Detected level in further validation batches.

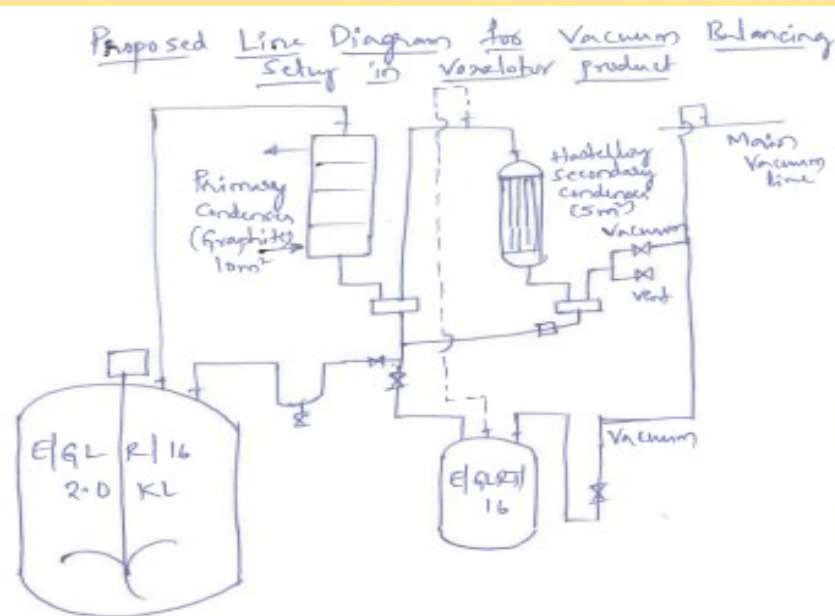
Troubleshooting

OOS in RS by HPLC during Trial batch in VOTB1 stage of Voxelotor

Product & Stage:	Voxelotor- VOTB1
Existing Situation	Requirement
OOS result was observed in Trial batch w.r.t. Related substances by HPLC test parameter.	Obtained ~1.20 RRT Impurity result is 1.51% (Limit NMT 1.50%), HIUI result is 0.83% (Limit NMT 0.30%), and Total Impurities result is 3.2% (Limit NMT 2.0%)

Proposal:

- 1) Based on Trial batch observations compared to kilo lab batches, Tri Fluoro Acetic acid + Trifluoro acetic Anhydride mixture distillation delay observed due to high vacuum requirement at lower temperature (below 45°C).
- 2) Vacuum balancing system with additional condenser (10 m²-Graphite MOC) was proposed to increase the rate of distillation & complete distillation below 48 hours.



Result:

Tri Fluoro Acetic acid + Trifluoro acetic Anhydride mixture Distillation completed in below 44 hours and quality was meeting the specification w.r.t. Related substances by HPLC in Trial-2 & Validation batches.

Capacity Enhancement

Product Name:
Pregabalin

Stage Code :

AMHA1: Additional streams included,

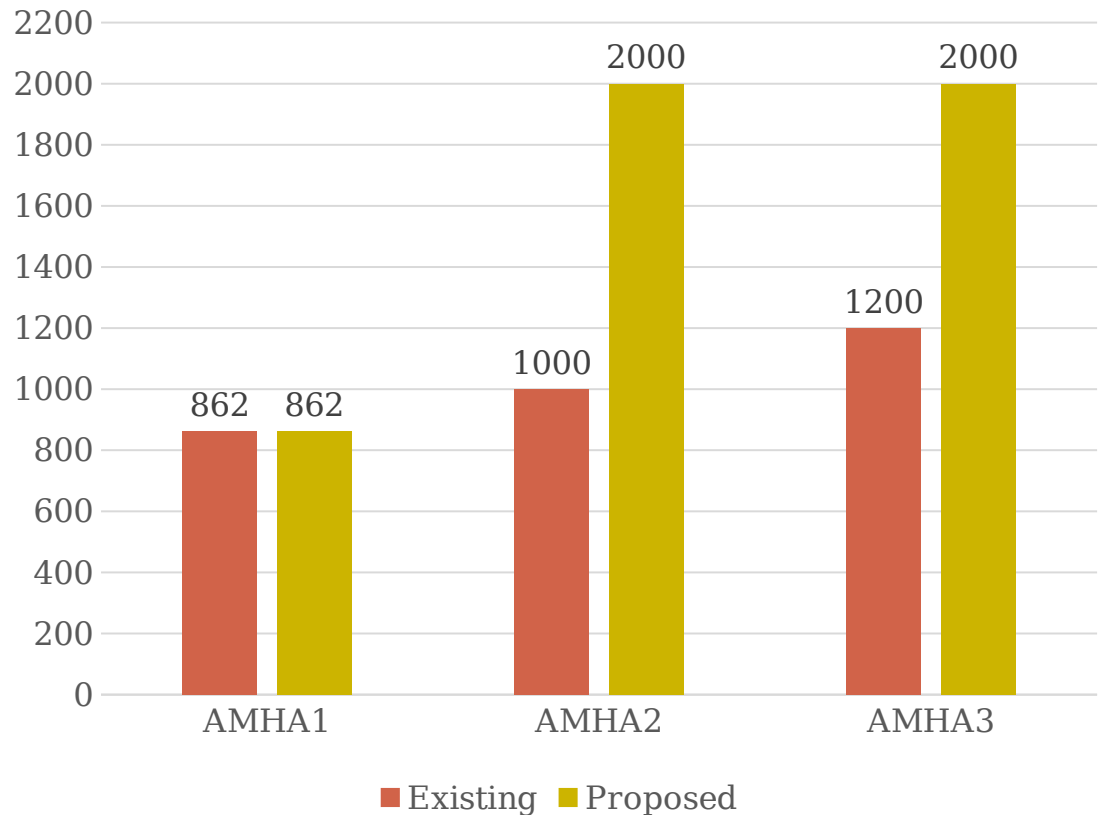
AMHA2: Scale-up from 1000 Kg in A-Block to 2000 Kg in C-Block & **AMHA3:** Additional streams included.

Block: A, B & C.

Existing : 18 to 20 TPM.

Proposed : 28 to 30 TPM.

AMHA1		AMHA2		AMHA3	
Existing	Proposed	Existing	Proposed	Existing	Proposed
862 kg	862 kg	1000 kg	2000 kg	1200 kg	2000 kg



Capacity Enhancement

Product Name:
Atorvastatin
Calcium

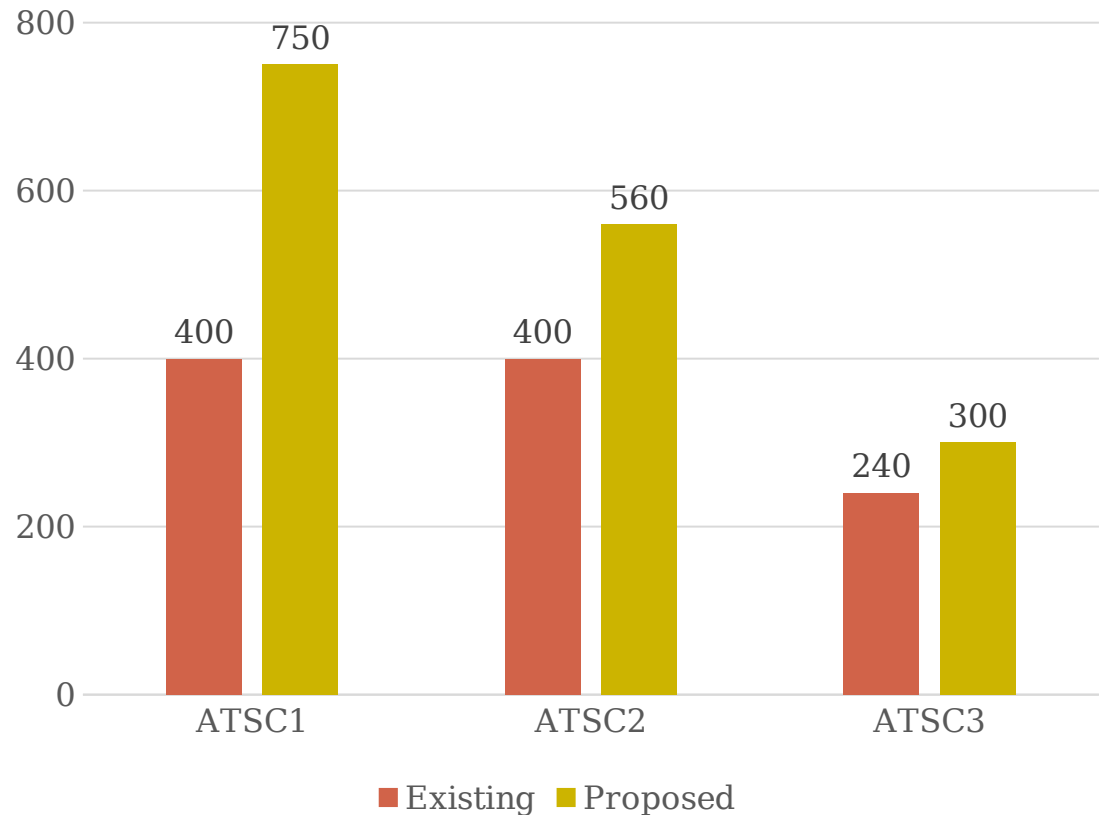
Stage Code : ATSC1,
ATSC2 & ATSC3.

Block: B & E.

Existing : ~4.2 TPM.

Proposed : ~8.4 TPM.

ATSC1		ATSC2		ATSC3	
Existing	Proposed	Existing	Proposed	Existing	Proposed
400 kg	750 kg	400 kg	560 kg	240 kg	300 kg



Capacity Enhancement

Product Name:
Rosuvastatin
Calcium (RA)

Stage Code : RVST1
& RVST2.

Block: E & B.

Existing : 1.7 TPM.

Proposed : 4.0 TPM.

RVST1		RVST2	
Existing	Proposed	Existing Phase-I	Proposed Phase-II
150 kg	350 kg	125 kg	300 kg



Capacity Enhancement

Product Name:

Ranolazine

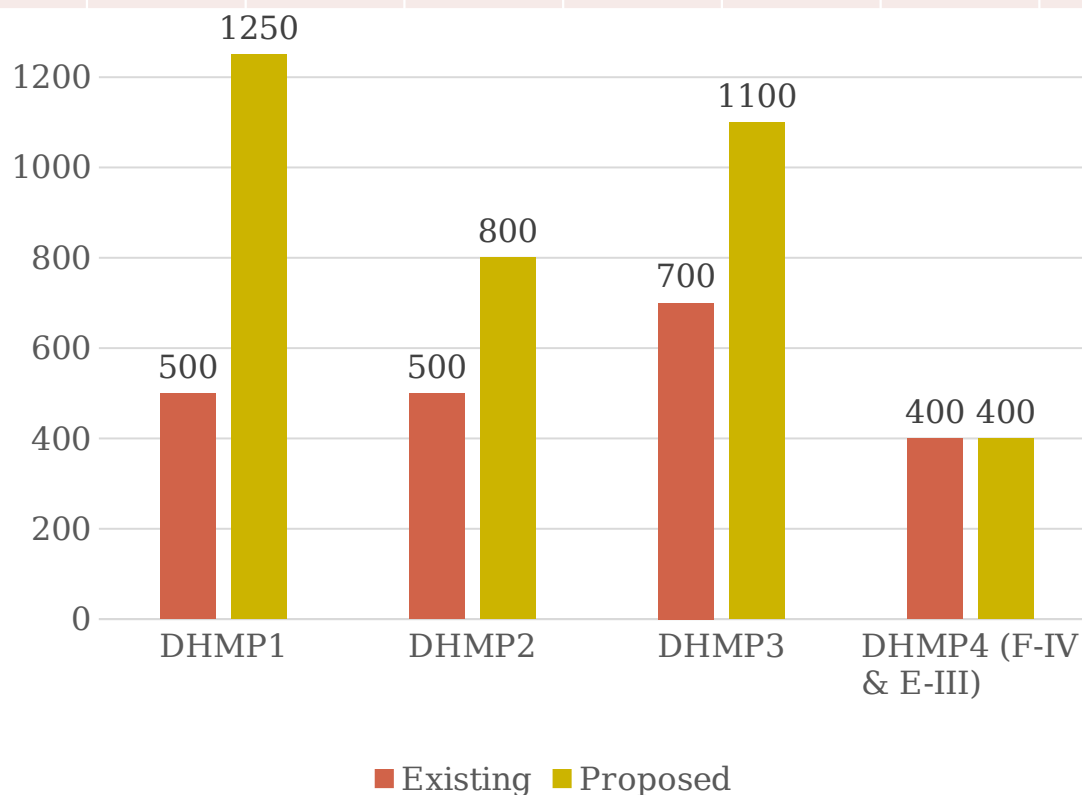
Stage Code : DHMP1 ,
DHMP2, DHMP3 &
DHMP4.

Block: B, C & E-III.

Existing : ~ 8.0 TPM.

Proposed : ~ 16.0 TPM.

DHMP1		DHMP2		DHMP3		DHMP4	
Existi ng	Propo sed	Existi ng	Propo sed	Existi ng	Propo sed	Existi ng	Propo sed
500 Kg	1250 Kg	500 Kg	800 Kg	700 Kg	1100 Kg	F-IV	F-IV & E- III
1400							



Capacity Enhancement

Product Name:
Levetiracetam
(Doc)

Stage Code : LVTC1
& LVTC2.

Block: B and E-IV&F-
IV.

Existing : ~ 8 TPM.

Proposed : ~ 40 TPM.

LVTC1		LVTC2	
Existing	Proposed	Existing	Proposed
400 Kg	800 Kg	450 Kg	800 Kg





New Products

SUCRALFATE

New Products

Sucralfate
Istradefylline
Voxelotor
Rimegepant
Sitagliptin (Enzyme Route)

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
SFTE1	T1	26-10-22	31-10-22	7.0	20.36	17.58 to 21.48
SFTE1	V1	19-11-22	23-11-22	7.4	23.2	18.59 to 22.71
SFTE1	V2	07-12-22	11-11-22	7.4	24.18	
SFTE1	V3	20-12-	25-12-	7.4	24.5	
Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
SFTE2	T1	15-12-22	21-01-23	20	34.55	31.80 to 38.8
SFTE2	V1	02-01-23	08-01-23	22	39.2	34.98 to 42.68
SFTE2	V2	11-01-23	17-01-23	22	35.2	
SFTE2	V3	18-01-23	24-01-23	22	37.1	



New Products

SUCRALFATE MICRONIZATION DETAILS

New Products

Sucralfate

PSD as per
Customer
requirement
D90 NMT : 15(µm)

SSA NLT : 4.

Micronization three
times trails done and
meet the customer
requirement.

Batch No	I/p (Kg)	O/p (Kg)	Top Sieved (Kg)	Loss Qty (Kg)	Samples Qty (Kg)
PSCFT 005122 2	14	11.2	1.2	1.28	0.32
PSCFT 006122	12.9	11.3 _q	0.23	1.055	0.195
Trail		D90 (µm)	D50 (µm)	D10 (µm)	SSA
Plain material		399	168	38.5	---
1st time Micronization		22.2	9.48	2.57	2.848
2nd Time Micronization		13.9	6.5	2.12	5.777
3rd Time Micronization		12	5.92	1.89	5.873



New Products

ISTRADefylline

New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme Route)

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
IDLE1	T1	03-12-22	03-12-22	7.00	8.00	6.44 to 7.98
IDLE1	V1	20-12-22	23-12-22	7.50	7.69	6.90 to 8.5
IDLE1	V2	28-12-22	31-12-22	7.50	8.94	
Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
IDLE2	T1	27-01-23	01-02-23	7.50	8.64	7.95 to 9.75
IDLE2	T1 (RP)	04-03-23	05-03-23	8.00	6.78	6.23 to 7.76
IDLE2	V1	22-03-23	04-04-23	7.50	7.78	5.50 to 8.50
IDLE2	V2	07-04-23	14-04-23	7.50	6.04	
IDLE2	V3	14-04-23	22-04-23	7.50	7.90	



New Products

ESTRADERYLLIN

New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme Route)

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
IDLE3	T1	14-04-23	17-04-23	6.50	5.12	5.07 to 6.18
IDLE3	V1	25-04-23	28-04-23	7.00	6.00	4.41 to 6.62
IDLE3	V2	04-05-23	06-05-23	7.00	5.70	
		07-05	10-05			
Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
IDLE4	T1	26-04-23	29-04-23	5.00	4.26	3.95 to 4.83
IDLE4	V1	16-05-23	19-05-23	5.50	5.00	4.35 to 5.31
IDLE4	V2	24-05-23	27-05-23	5.50	5.10	
IDLE4	V3	01-06-23	03-06-23	5.50	5.10	



New Products

VOXELOTOR

New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme Route)

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
VOTR 1	T1	02-11-22	06-11-22	40	67.9	59.2 to 72.4
VOTR 1	V1	29-11-22	02-12-22	42	71.1	62.16 to 76.02
VOTR 1	V2	08-12-22	12-12-22	42	72.1	
Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
VOTR 2	T1	24-11-22	28-11-22	10	9.8	8.2 to 10.0
VOTR 2	T2	06-12-22	16-12-22	57	46.3	46.74 to 57
VOTR 2	RP	--	19-02-23	25.45	18.82	---
VOTR 2	V1	06-01-23	12-01-23	70	66.6	57.4 to 70.0
VOTR 2	V2	13-01-23	22-01-23	70	66.0	
VOTR		30-01-	29-01-			

New Products



New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme
Route)

VOXELOTOR

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
VOTR 3	T1	07-01-23	12-01- 23	45	39.5	34.65 to 42.3
VOTR 3	RP	--	--	39.5	34.7	--
VOTR 3	V1	23-02-23	04-03- 23	63	57.5 4	48.51 to 59.23
VOTR 3	V2	02-03-23	13-03- 23	63	57.5 0	
VOTR 3	V3	07-03-23	17-03- 23	63	57.3 0	

New Products



RIMEGEPANT

New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme Route)

Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
RMGS 1	V2	07-04- 23	15-04- 23	310	221.5 1	226.92 to 277.35
RMGS 1	V3	14-04- 23	23-04- 23	310	221.2 0	

Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
RMGS 2	V1	09-04- 23	15-04- 23	255	201.0 8	170.70 to 206.37
RMGS 2	V2	18-04- 23	24-04- 23	255	183.1 9	
RMGS 2	V3	25-04- 23	02-05- 23	247	163.4 5	
RMGS 2	V3 (Lot- 1 RP)	20-05- 23	21-05- 23	91.5	69.95	--



New Products

RIMEGEPANT

New Products

Sucralfate
Istradefylline
Voxelotor
Rimegepant
Sitagliptin (Enzyme Route)

Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
RMGS 3	V1	18-04- 23	27-04- 23	130	75.47	70.20 to 85.80
RMGS 3	V2	28-04- 23	07-05- 23	230	129.7	124.20 to 151.80
RMGS 3	V3	26-05- 23	03-06- 23	189	101.4	102.06 to 110.76
Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
RMGS 4	V1	29-04- 23	08-05- 23	125	102.2 4	85.00 to 103.75
RMGS 4	V2	12-05- 23	22-05- 23	125	119.7	
RMGS 4	V3	08-06- 23	18-06- 23	129. 3	118.4	87.92 to 107.32



New Products

SUCRALFATE (Enzyme Route)

New Products

Sucralfate
Istradefylline
Voxelotor
Rimegepant
Sitagliptin (Enzyme Route)

Stage	Trail / Validation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
SATM1	T1	08-06-23	13-06-23	100	122.43	105.00 to 129.00
SATM1	T2	21-06-23	26-06-23	450	601.16	472.52 to 580.48
SATM1	V1	07-07-23	13-07-23	450	595.73	540.90 to 613.04
SATM1	V2	11-07-23	17-07-23	450	591.28	
SATM1	V3	16-07-23	22-07-23	450	598.32	



New Products

Sitagliptin (Enzyme Route)

New Products

Sucralfate

Istradefylline

Voxelotor

Rimegepant

Sitagliptin (Enzyme Route)

Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
SATM2	T1	17-06-23	23-06-23	122	144.2	145.18 to 176.90
SATM2	T2	03-07-23	12-07-23	550	649.1	654.50 to 797.50
SATM2	V1	20-07-23	26-07-23	550	666.48	584.65 to
		24-07				
Stage	Trail / Valid ation	Start Date	End date	I/P (Kg)	O/P (Kg)	Yield Range (Kg)
SATM3	T1	10-07-23	16-07-23	143	93.74	105.82 to 130.13
SATM3	T2	26-07-23		450		333.00 to 409.50

TECHNICAL SUPPORT

Equipment Mapping & Facility Creation:

- 6.0 KL Hydrogenation Reactor facility created in B-Block for ATSC1 stage of Atorvastatin calcium and scale-up batches execution completed with Input 400 Kg, 600 Kg & 750 Kg.
- Azeotropic Set-up arranged for Oseltamivir Phosphate for water removal.
- Vacuum balancing set-up arranged to F/SSR/03 (4 KL) in F-Block for Rosuvastatin Calcium Pharma Stage.
- Vildagliptin Stage-1 Modified process Execution at 40 Kg Scale completed. Scale-up to be executed after receiving new 1.0 KL Halar Lined PNF.
- Rosuvastatin Ca. Single stage process for IP-Execution completed with 75 Kg Batch Size, Scale-up to be planned.
- Additional streams in Pregabalin RM route for capacity enhancement from 4.5 TPM to 10 TPM.
- MDC Solvent Recovery improved in Pantaprazole by implementing brine circulation for Primary condenser.

TECHNICAL SUPPORT

Troubleshooting:

- Pregabalin Flowability requirement for M/S Zentiva- Sifting Trials u/process to achieve desired nature.

New Production Blocks:

- I-Block equipment's i.e., Filtration and Drying equipment's modified as per Mr. Vithal sir instruction.
- Accessories requirements finalized for G-Block & D-Blocks.
- Utility load (CT water, Chilled Water & Chilled Brine etc.) for new Production blocks.

New Proposal



- Experiments conducted for Hydrolysis Reaction to avoid frothing and to increase batch size in PREGABALIN (AMHA1) in heating condition. Process Finalized with Reverse addition at 70-75°C & Scale-up batches upto 500 Kg B.Size executed in Plant.
- ANFD Filtration & Drying trail conducted to reduce the drying time cycle in Atorvastatin Calcium (ATSC3), slow filtration and hard lumps observed.
- RCVD trail for Atorvastatin Calcium (ATSC3) for drying to be plan.
- Homogenizer trails planning for Atorvastatin Calcium.
- Flow Chemistry Experiment Trials conducted for Enzyme Reaction & Amidation reaction of Pregabalin Stage-2.

MSN
LIFE SCIENCES-
III
Bhiknoor.